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Mapping attention-deficit/hyperactivity disorder from childhood to adolescence - no neurophysiologic evidence for a developmental lag of attention but some for inhibition

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Abstract: **BACKGROUND:** The role of a developmental lag for deficits of higher brain functions in attention-deficit/hyperactivity disorder (ADHD) has not yet been tested in longitudinal studies. We examined the development of neurophysiological markers of attention (Cue P300; contingent negative variation [CNV]) and inhibition (NoGo P300) in ADHD and control groups from childhood to adolescence for support of the developmental lag hypothesis of ADHD. **METHODS:** ADHD (n = 28/3 girls) and control (n = 22/5 girls) subjects were assessed at baseline (Time 1; ADHD age 10.8 +/- 1.8 years, controls 10.4 +/- 1.1 years) and at two follow-up examinations (Time 2 after 1.2 years, Time 3 after 2.5 years). Event-related potential maps were recorded during a cued Continuous Performance Test (CPT) at all assessments and analyzed using scalp and source (sLORETA) measures. **RESULTS:** CPT performance showed common effects of ADHD and younger age, consistent with (but not specific to) developmental lag. The NoGo P300 developed earlier and became stronger in control subjects than in the ADHD group, again consistent with an initial developmental lag. In contrast, the attenuation of the Cue P300 and the CNV with ADHD at all assessments was opposite to the enhancement with younger age and thus inconsistent with developmental lag. The sLORETA source localization also differed between ADHD and developmental effects. **CONCLUSIONS:** These results provide strong evidence for multiple and persistent neural processing deficits in ADHD. They do not support the developmental lag hypothesis for attentional dysfunction in ADHD despite partial evidence that developmental lag contributes to inhibitory brain dysfunction during early adolescence.

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Title

Mapping attention-deficit/hyperactivity disorder (ADHD) from childhood to adolescence – no neurophysiological evidence for a developmental lag of attention but some for inhibition

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Abstract

Background: The role of a developmental lag for deficits of higher brain functions in ADHD has not yet been tested in longitudinal studies. We examined the development of neurophysiological markers of attention (Cue P300, CNV) and inhibition (NoGo P300) in ADHD and control groups from childhood to adolescence for support of the developmental lag hypothesis of ADHD.

Methods: ADHD (N=28 / 3 girls) and control (N=22 / 5 girls) subjects were assessed at baseline (time 1; ADHD age 10.8 ± 1.8 years, controls 10.4 ± 1.1 years) and at two follow-up examinations (time 2 after 1.2 year, time 3 after 2.5 years). Event-related potential (ERP) maps were recorded during a cued Continuous Performance Test (CPT) at all assessments, and analyzed using scalp and source (sLORETA) measures.

Results: CPT performance showed common effects of ADHD and younger age, consistent with (but not specific to) developmental lag. The NoGo P300 developed earlier and became stronger in controls than in the ADHD group, again consistent with an initial developmental lag. In contrast, the attenuation of the Cue P300 and the CNV with ADHD at all assessments was opposite to the enhancement with younger age, and thus inconsistent with developmental lag. The sLORETA source localization also differed between ADHD and developmental effects.

Conclusions: The results provide strong evidence for multiple and persistent neural processing deficits in ADHD. They do not support the developmental lag hypothesis for attentional dysfunction in ADHD despite partial evidence that developmental lag contributes to inhibitory brain dysfunction during early adolescence.

Keywords

ADHD, children, NoGo P300, Cue P300, CNV, developmental lag, sLORETA

Introduction

ADHD (attention deficit hyperactivity disorder) is the most frequently diagnosed childhood psychiatric disorder (5.24% prevalence; 1). The core symptoms of inattention and impulsivity/hyperactivity severely limit the affected children and their environment in school and at home. Because higher levels of motor activity and poorer performance on attention tests (2) also characterize younger children, a developmental lag of cognitive functions (3) has long been hypothesized to underlie ADHD. Some support for a role of developmental lag comes from longitudinal studies of ADHD children and adolescents where categorical ADHD diagnoses suggest considerable remission, but age-standardized behavioral scores exhibit far less remission (4). Recent longitudinal MR work implicates developmental lag and suggests that structural maturation of cortical thickness is delayed by about 3 years in ADHD, with particularly prominent delays in frontal and temporal cortex regions (5).

Such regional developmental lag may relate to Posner and Petersen's (6) model of independent neural networks and neuromodulators subserving different attentional functions. Inattention and impulsivity have consistently been linked to deficits of the distinct brain systems responsible for attention and for inhibitory control. Posner et al. (7) review evidence that while posterior structures (superior parietal, temporal parietal junction, frontal eye fields etc.) dominate in attentional orienting, both frontal and posterior areas contribute to attention alerting, and mainly anterior structures are involved in executive functions such as inhibition (anterior cingulate cortex, lateral ventral cortex, prefrontal cortex etc.). ADHD children exhibit deficits in all three systems (8). The reduced frontal activation in ADHD during inhibition tasks has been linked to similar frontal reductions in younger subjects (9) which are reduced in attention tasks in support of a prefrontal developmental lag (10). However, developmental trends appear task dependent, as increased frontal activity in younger subjects has also been found with other inhibition task (10, 11), along with evidence for shifts from diffuse to more focal activity (12, 13) and for fine tuning within an activated network (14).

Some functional MRI studies also revealed that ADHD children had more frontal activation in inhibition tasks (15, 16), suggesting that frontal hypoactivation in ADHD is task-dependent and may be offset by compensatory frontal processes.

Attention-sensitive components of the event-related potential (ERP) reflect the time course of activation in these systems. In ADHD children, impaired attention is reflected in a reduction of the P300 to attended items such as rare targets, or cues signalling an upcoming Go-NoGo task (17, 18). Because cues already require attentional orienting and preparation but no response, the cue P300 is not confounded by action-related processes (19). Source localization of the cue P300 implicates posterior brain areas (19, 20, 21).

Attentional ERP components typically increase during childhood but subsequently decrease during adolescence (Target P300 peaking at around age 11 in visual tasks; 22, 23, 24). Given such nonlinear developments (25) which also characterize cortical thickness (5), effects of ADHD due to a developmental lag may even reverse with age (Figure 1). Distinct patterns may thus reflect developmental lag at different phases of maturation, and closely spaced longitudinal tests from more than two time points are needed to detect subtle nonlinear development.

Developmental lag implies that within a certain time window developmental trajectories are of normal shape but delayed. Thus, normal values will be obtained later. Since the concept does not preclude age limits for development, there is the possibility that ADHD subjects never outgrow the delay. Thus, we distinguish between persistent developmental lag, transient developmental lag, and developmental deviation where normal values are never obtained (Figure 1).

*** Figure 1 (developmental lag) ***

ADHD is also characterized by an inhibition deficit (26). Deficits in response control and inhibition are reflected by reduced NoGo P300 activity in children (27, 28, 29, 30) and adults suffering from ADHD (31). Source estimation localizes this NoGo P300 and its reduction in ADHD to prefrontal regions (21, 32), particularly to the anterior cingulate cortex (ACC). However, developmental trends from childhood to adolescence appear inconsistent or task dependent, as some evidence suggests a late development of the NoGo P300 after age 9 (33), while others find a more prominent frontal NoGo P300 at age 9 than 11 (34).

Attentional deficits of ADHD children during preparation periods are also implicated by reduced amplitudes of the contingent negative variation (CNV; 35, 36, 37). This ERP component is related to brain processes of selective preparation and time estimation (38, 39) and has both frontal and posterior sources (40). Developmental CNV studies suggest that while frontal aspects of the early CNV still develop in adolescence, the late CNV is already mature before age 10 (41, 42).

In summary, ERP studies implicate a number of separable attentional subsystems with distinct sources. In addition, cross-sectional studies reveal prominent, partly nonlinear developments of activity in these systems between childhood and adolescence which are important to test developmental lag models of ADHD, but no longitudinal ERP studies have yet compared trajectories of functional neural markers in ADHD and control groups.

Our longitudinal study examined the development of Cue P300 effects in ADHD and control groups in an age range in which P300 effects are established in ADHD children, and in which developmental lag should result in increased rather than reduced P300 amplitudes.

Additionally, we investigated the developmental and ADHD effects of NoGo P300 as a neurophysiological correlate of inhibition control and CNV as a correlate of preparation, time estimation and working memory. Results are discussed in relation to the developmental lag hypothesis of ADHD. Previous reports based on our sample dealt with the course of behavior and psychopathology (4) and neuropsychology (43) and concluded that developmental lag can

only partly explain ADHD children's deficits. Hence, we investigated whether a similar principle applies at the neurophysiological level, and examined the role of developmental lag and deviations for specific electrophysiological ADHD markers.

Methods and materials

The study investigated the longitudinal course of neurophysiological markers of attention in ADHD and control children. ADHD children and controls were recruited in Zurich from an epidemiological field study (1), from self-help organizations of parents with hyperactive children, from normal schools, and from our patients. Children with neurological disorders or with $IQ < 80$ had been excluded from the study. Children on stimulant medication suspended treatment at least 48 hours before testing (about 50% of ADHD subjects, see 4).

The three assessments consisted of the baseline (time 1) and two follow-up examinations after approximately 1.2 year (time 2) and 2.5 years (time 3). The diagnosis of ADHD was based on a structured interview conducted with the mothers or fathers (DISC 2.3; 44) at time 1 by trained undergraduate students according to DSM-III-R criteria, which was repeated at time 3 to assess persistence. Details regarding IQ testing, validation of diagnoses based on additional information by board certified clinicians, and the multiple informant approach used for both groups have been fully reported in previous publications dealing with this longitudinal study (4, 43). Group characteristics are shown in table 1.

*** Table 1 (group characteristics) ***

The control children had no psychiatric diagnoses while 12 ADHD children had comorbid oppositional defiant disorder and two had comorbid conduct disorder.

ADHD children scored significantly higher than controls in the DISC interview (hyperactivity/impulsivity and for inattention scores), and on the child behavior checklist at

all assessments (CBCL, filled out by the parents, see 4; scales for attention problems including hyperactivity items, and summary scales for externalizing and internalizing problems are reported here). Their IQ was also significantly lower, but neither age nor gender distribution showed any significant differences between the two groups.

These demographic, cognitive and psychiatric characteristics closely resembled those of our previous clinical publication (4), thereby confirming that these subgroups with complete brain mapping data remained well matched and showed the same severity and high persistence of ADHD symptoms as the full groups.

Event-related potential (ERP) maps were recorded during a validated cued CPT A-X (19) including rare cued Go and NoGo conditions embedded in a vigilance task with frequent distractors to assess both attentional and inhibitory processes. Letters were presented for 150 ms in pseudo-randomized order every 1.65 s at the center of a monitor and at a viewing distance of 120 cm and subtended approx. 5 degrees. The letter A (20% probability) served as a cue signaling a Go-NoGo task and inducing response preparation. Children pressed a mouse button with the index finger of their dominant hand as fast as possible every time the letter A was followed directly by the letter X (A-X target sequence, 10% probability), but had to withhold responses to A-not-X sequences (NoGo trials, also 10%). Note that the frequent uncued distractors which also require no response but no response inhibition are not part of the NoGo condition.

The 32-channel EEG and EOG were recorded with 256 Hz/channel (0.1 - 70 Hz, technical zero baseline). After artifact rejection, averaged stimulus-locked ERP map series were computed and transformed to the average reference. We used only correct trials for averaging. Microstates were determined by adaptive segmentation of the grand mean across both groups and all (uncued and cued) conditions (19, 45). Two P300-microstates (266-414 ms and 414-574 ms) after the Cue (A) and after NoGo (A-Not-X) were selected for brain mapping

analysis. Mean amplitude of the contingent negative variation (CNV) 1000-1600 ms following cues was analyzed. Amplitude was computed as Global Field Power (GFP), the root mean square of all voltages in a map (45). Tomographic source activity was analyzed using sLORETA (46).

For statistical CPT Performance analysis, (M)ANOVAs of false alarms (=commission errors), hits (=40 minus omission errors), reaction time (RT) and its standard deviation (RT-SD) were performed and followed by post-hoc t-tests.

For statistical ERP analysis, repeated measures ANOVAs of mean GFP in a given microstate were run for all conditions and followed by post hoc t-tests. To test specific topographies, i.e. whether reduced occipital amplitudes characterize the cue P300 and reduced central amplitudes the NoGo P300 and the CNV of both ADHD children and younger children, *t*-maps were computed for the effects of both ADHD (ADHD “minus” control children) and developmental lag (younger “minus” older children, that means, for instance, parameter at T1 “minus” parameter at T3 of the same group). In addition, supplementary ANOVAs of peak amplitudes and latencies (at Pz for the Cue P300, and at Cz for the NoGo P300) were computed to examine also development x ADHD interactions.

Standard statistical assessments of CPT performance and GFP are reported without covarying for IQ, whereas analyses with IQ as a covariate are presented in the supplementary material.

Discrepancies are discussed in the text.

Results

CPT performance

Development of CPT performance is shown in Figure 2. Hit rates increased with age, and ADHD subjects had lower hit rates than controls at all assessments (in other words: ADHD subjects displayed more omission errors than controls).

False alarms (commission errors) tended to decrease over time. ADHD subjects made significantly fewer false alarms in the second than in the first assessment. False alarms of controls appeared stable over time. ADHD subjects made significantly more false alarms than controls at all assessments.

Reaction time decreased with age. ADHD subjects were slower than controls; this was significant at the second and third assessment and increased with age.

RT-SD decreased with age in the ADHD group. Control subjects showed a peak of RT-SD at time 2 and smallest values at time 3. Controls displayed lower RT-SD than ADHD subjects at all three assessments.

Multivariate statistics with IQ as covariate revealed a significant effect for IQ (Supplementary Table 1). Univariate analyses with IQ as covariate showed a significant time effect for hit rate and trends for group effects concerning false alarms and reaction time. Effect of IQ was significant for hit rate.

*** Figure 2 (CPT performance) ***

Segmentation of the ERPs

Adaptive segmentation based on the grand mean ERP over all conditions and all subjects yielded two microstates in the P300 and one in the CNV time range (see Figure 3). We focused on Cue P300, NoGo P300, and CNV for the brain mapping analyses. The microstates for the time frame 266-414 ms and 414-574 ms corresponded to conventional P300 ERP components and were labelled P3a and P3b. The corresponding waveshapes at selected electrodes for both groups and all 3 assessments are shown in Supplementary Figure 1.

*** Figure 3 (Adaptive segmentation) ***

Cue P300

ADHD children had less GFP (map strength) than controls (*group effects for Cue P3a* [$F(1,48)=15.098, p=0.001$] and *Cue P3b* [$F(1,48)=14.303, p=0.001$]). Unlike ADHD subjects, younger children had more GFP than older children (*time effect for Cue P3b* [$F(2,47)=11.268, p=0.001$]). These group and time effects interacted for the P3b ($F(2,47)=3.376, p=.043$) due to an increased group difference at T2, as illustrated along with the post hoc comparisons in Supplementary Figure 2a. The group by time interaction remained significant for P3b and became significant for P3a if IQ was used as covariate. As a result, the *t*-maps characterizing ADHD children (ADHD „minus“ control children) and those characterizing younger children (younger „minus“ older children; T1 minus T3) showed roughly opposite polarity, particularly for the P3b microstate where opposite effects of ADHD and younger age were significant at posterior and frontal sites (Figure 4).

Analyses of Cue P300 peak latencies and amplitudes are shown in Supplementary Table 2a. Decreasing latency with age (main effect for time) and reduced amplitudes in the ADHD group were observed (main effect for group, significant post hoc *t*-tests). Control subjects amplitudes peaked at the second assessment which corresponds to the typical nonlinear P300 development.

*** Figure 4 (Cue-P3b maps/t-maps/sLORETA) ***

sLORETA

Tomographic analyses by sLORETA revealed superior parietal sources of cue P300 for all times and both groups (Supplementary Figure 3a). Significant differences between both groups were localized superior parietal at time two and are found in right temporal region at time three. ADHD subjects showed reduced activity compared to controls in these regions (Figure 4).

CNV

The ADHD group had less CNV-GFP than controls (*group* [$F(1,48)=13.693, p=0.001$]), while younger children had more CNV-GFP than their older peers (*time* [$F(2,47)=13.067, p=0.001$], *interaction with group n.s.*, *illustrated along with the post hoc comparisons in Supplementary Figure 2b*). The group effect remained significant even if IQ was used as a covariate (Supplementary Figure 2b).

The ADHD effects illustrated by the *t*-maps were significant for the frontal positivity and the central negativity at second and third assessments (most pronounced for the second assessment). The developmental CNV amplitude reduction was significant only for the frontal positivity, where the effects of ADHD and younger age (T1 minus T3) showed roughly opposite polarity (Figure 5). Tomographic analyses by sLORETA revealed posterior cingulate cortex (PCC) sources of CNV for second and third assessment and both groups (Supplementary Figure 3b). Significantly reduced activity in the ADHD group was localized to right superior parietal areas at time two and to superior parietal regions at time three (Figure 5).

*** Figure 5 (CNV maps/t-maps sLORETA) ***

NoGo P300

ADHD children had less GFP than controls in both NoGo P300 microstates, while younger children had more GFP than older ones in the NoGo P3b microstate. The effects of development and ADHD interacted for the NoGo P3a GFP which decreased in ADHD children with age while group differences increased with age (*NoGo P3a: group* [$F(1,48)=12.427, p=0.011$]; *group x time* [$F(2,47)=3.714, p=0.032$]; *NoGo P3b: group* [$F(1,48)=16.303, p=0.001$]; *time* [$F(2,47)=5.445, p=0.007$]). These effects are illustrated

along with the post hoc comparisons in Supplementary Figure 2c. Main effects for group remained significant, and group by time interaction for P3a showed a trend with IQ as a covariate.

The NoGo-P3a topography developed from an “immature” parietal towards the typical central positivity (Figure 6). This central positivity is already present at T1 for the controls, but not before T3 for the ADHD group. The *t*-maps illustrate that the developmental effect for the NoGo P300 is particularly prominent in this age range and similar for both groups, with highly significant increases at frontocentral and decreases at posterior electrodes. The *t*-maps characterizing the ADHD effect showed an increasing difference between ADHD and control subjects with age at frontal, central and temporal sites which strongly resembles the developmental effects.

Analyses of NoGo P300 peak latencies and amplitudes (Supplementary Table 2b) revealed decreasing peak latencies with age (time main effect) as well as significant group differences concerning peak amplitude (group main effect). Post hoc *t*-tests showed significant group differences for NoGo P300 amplitude at all assessments.

*** Figure 6 (NoGo P3a maps/*t*-maps/*s*LORETA) ***

*s*LORETA

Source localization using tomographic analyses by *s*LORETA revealed right inferior parietal sources for both groups and for first assessment as well as second assessment for ADHD subjects. Occipital sources characterized control subjects at second and ADHD subjects at third assessment. Source localization of the NoGo P3a revealed an ACC activation only for control subjects at third assessment (Supplementary Figure 3c). Significant group differences

were also found at the third assessment, with ADHD subjects showing reduced posterior activity compared to controls (Figure 6).

Discussion

For these longitudinally studied ADHD children, performance measures and neural measures of inhibitory processing derived from the cued CPT at least partly supported the developmental lag hypothesis, but neural measures of attentional processing proved incompatible with a developmental lag explanation of ADHD.

CPT performance of ADHD subjects was clearly poorer compared to controls concerning hit rate, false alarms, reaction time and its standard deviation at all three assessments (except for a non-significant reaction time difference at T1). The developmental effects (higher hit rate and faster reaction time with age) are consistent with the literature (e. g. 7). None of the ADHD-related performance problems became less significant with development, although one expects reduced group differences with further development at least for error measures due to ceiling effects. The similar pattern of performance deficits for ADHD and younger children is thus consistent with a developmental lag model of ADHD for the age-range covered here.

The neural effects, however, provide a more differentiated picture. The reduced cue P3a and P3b in the ADHD group suggests impaired attentional orienting or resource allocation, and replicates our previous findings (19). The fact that this amplitude reduction showed minimal variation (peaking at T2 for the P3b) but did not diminish over follow up assessments indicates a largely stable deficit over the 2.5 years covered by the present study. This developmental continuity of the ADHD effect was accompanied by a significant decrease of the cue P3b itself, which agrees with cross-sectional results for the target P300 in this age

range (22, 23). The developmental cue-P3b decrease was similar in both groups, which suggests normal maturation of posterior attention functions despite attenuation in ADHD. Importantly, these effects of ADHD and those of younger age were opposite in terms of GFP and topography. Such distinct patterns of neural deviation are inconsistent with either transient or persistent developmental lag.

Cue P300 activity localized to superior parietal brain areas for both groups. ADHD children displayed reduced activity localized to superior parietal regions at second assessment, which might be associated with deficits in orienting (7, 47). ADHD subjects also showed reduced localized activity in the right temporal regions at the third assessment, which might be associated with impaired visual integration (48). These results are in accordance with previous findings (8) that attention orienting and reorienting is achieved by a network lateralized to the right temporo-parietal cortex and to the right inferior frontal gyrus and modulated by the cholinergic system (49).

The reduced CNV activity in ADHD children at second and third assessment suggests preparation deficits. These deficits became more pronounced at the second assessment and were still significant at the third assessment. The CNV showed minimal developmental effects and can be regarded as a stable marker independent of age in this (limited) age range, consistent with Segalowitz et al. (50) and Jonkman et al. (41), who found comparable late CNV amplitudes for children and adults, despite some developmental changes in CNV topography similar to those in Bender et al. (51) were evident. This constellation contradicts a transient developmental lag of CNV for ADHD children.

The reduced NoGo P300 activity in ADHD children at all assessments during this phase of prominent developmental increase suggests abnormal brain activation during inhibitory performance, which remain stable with development in this age range, and may suggest a persistent developmental delay. This agrees with our behavioral findings showing similar

persistence of elevated scores on multiple CBCL scales, and of higher interview-derived inattention and hyperactivity/ impulsivity scores for the ADHD compared to the control group of this sample (4), even though earlier work had suggested a more prominent remission of behavioral impulsivity than of inattention scores (52). The findings also confirm that the cued CPT contains a well validated Go-NoGo task (53, 54, 55, 56), and that a lower probability of the NoGo condition is not critical for typical anterior NoGo P300 topographies (57, 58). Still, the inhibitory load on NoGo trials of this cued CPT is somewhat lower than in typical Go-NoGo tasks, where Go probabilities of about 70% also require suppressing habitual, high probability responses. It thus remains open how well our conclusions would hold under increased inhibitory load, and to what extent our NoGo P300 reflects conflict and error monitoring processes in addition to inhibition. However, our typical frontocentral NoGo P300 topography and tomography agrees with classical Go-NoGo and stop tasks. It differs from the small response to distractors as well as from the more posterior Cue and Go P300. The current NoGo P300 is thus unlikely to reflect mainly selective attention effects. Most importantly, the NoGo P300 shows different developmental trajectories of the ADHD related deficits than the Cue P300.

Tomographic source localization of the NoGo P3a revealed different sources. The ACC source localization which was established at third assessments for control subjects is consistent with adult studies of Fallgatter et al. (59). ADHD subjects showed reduced localized activity in occipital regions compared with healthy controls, which might be associated with impaired visual attention in this task.

The NoGo P3a maps and source localizations of younger controls were similar to those of older ADHD subjects, and the t-maps of the effects of ADHD and of younger age were strikingly similar, consistent with a developmental lag. However, as the NoGo P300 attenuation of ADHD children still increased with age, future research must clarify whether

these differences eventually also disappear once maturation is complete (according to a transient developmental lag) or whether they remain stable according the persistent developmental lag model.

In conclusion, our findings demonstrate a striking persistence of behavioral and neural deficits, and suggests that developmental lag plays a role for inhibitory but not for attentional ADHD-related processing deficits.

We found no evidence that younger children's and ADHD children's attentional brain processes related to orienting and preparation are alike, as predicted from the developmental lag theory. Group differences even increased with age, which makes it unlikely that a maturational lag contributes to these deficits during other developmental periods. Attenuated or deviant development seems a better explanation for these results.

On the other hand, performance deficits and the delayed initial development of the NoGo P300 support a developmental lag of response inhibition. The different clinical picture of ADHD in childhood and adolescence might be a correlate of such distinct developmental courses of different brain functions.

Most group differences persisted or even increased in early adolescence, consistent with findings that ADHD often persists into adulthood, and that these adult ADHD patients continue to suffer from both attentional and inhibitory deficits including a NoGo P300 attenuation (31). This poses a problem for the classical transient developmental lag models which predict that deficits become smaller and disappear with brain maturation. However we have to consider the possibility of a persistent developmental lag that is never outgrown.

We propose that the developmental lag model might reasonably be modified by adding the assumption that late maturation terminates at around the same age for all groups, and thus before the clinical group has fully caught up. Future studies should follow the developmental trajectories of those brain functions which are impaired in ADHD into adulthood. It will be

essential to clarify which of these ADHD markers show developmental continuity into adulthood, and which ones are replaced by other markers of dysfunction. Full normalization of neural function seems less likely in the light of the high rate of persistence of ADHD into adulthood.

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Table / Figure Legends

Figure 1. Developmental lag effects depend on the shape of the maturation trajectories (schematic, black line = healthy controls, dotted line = clinical group with developmental lag or deviation). Four different models are pictured: Transient developmental lag means that the clinical group grow out of its delay; Persistent developmental delay means that the developmental trajectory is consistent with developmental delay, but the clinical group never grow out of its delay; Discontinuous developmental delay - while a monotoneous increase results in continuity of both developmental lag and group effects, an initial peak followed by decrease (as for example reported for target P300 amplitudes) leads to a reversal of the developmental lag and group effects around the peak. For both models (continuous and discontinuous), developmental lag effects start once a given marker is present in both groups and resolve once maturation is complete or the developmental delay persists. Developmental deviation means different developmental trajectories for healthy group versus clinical group.

Table 1. Group characteristics

Figure 2. CPT performance including repeated measures ANOVA and post-hoc *t*-Tests (pictured in the figure using asterisks)

Figure 3. Adaptive segmentation and resulting microstates in the CPT of the grand mean of both groups based upon averaging the neuroelectrical activity evoked by all stimuli. Red vertical lines indicate the microstate borders. The dotted vertical line indicates stimulus onset.

Figure 4. Cue P3b - topographic maps, *t*-maps and sLORETA source localization (*t*-maps depict the differences between the first and the last assessment (T1- T3) and between both

groups (ADHD – controls), respectively. sLORETA statistics comparing the Cue-P3b-related activation for ADHD and control subjects at all assessment. Blue color indicates the localization of significantly reduced activity of the ADHD children compared to controls. Endpoints of scales for group comparison meet significant log of F-ratios at $p < 0.05$ for the two-tailed test, SNR 100)

Figure 5. CNV - topographic maps, *t*-maps and sLORETA source localization (*t*-maps depict the differences between assessments and between both groups, respectively. sLORETA statistics comparing the CNV-related activation for ADHD and control subjects at all assessment. Details as in Fig. 4)

Figure 6. NoGo P3a - topographic maps, *t*-maps, sLORETA source localization (*t*-maps depict the differences between assessments and between both groups, respectively. sLORETA statistics comparing the NoGo-related activation for P3a microstate of ADHD and control subjects at all assessment. Details as in Fig. 4)

Figure 1

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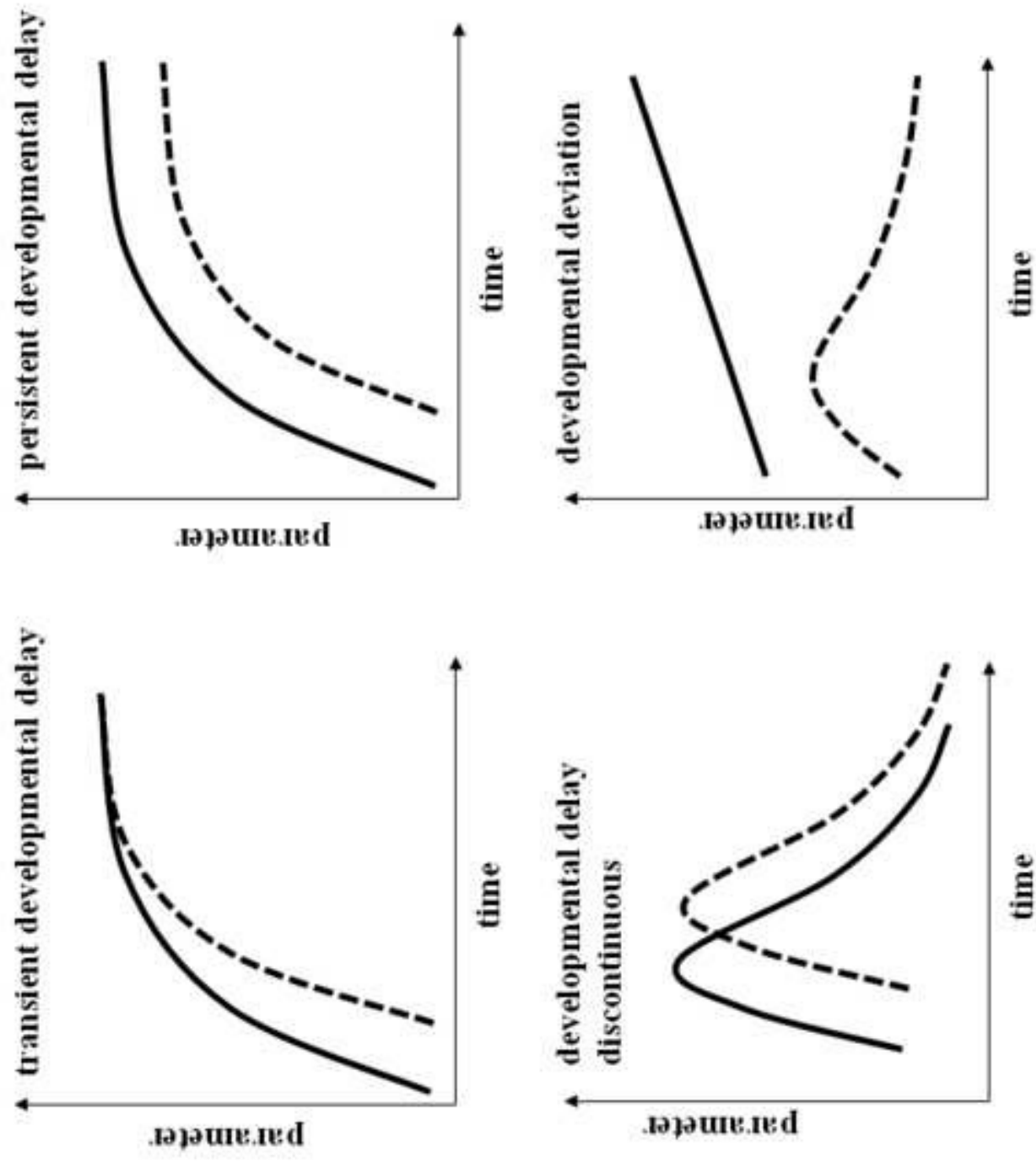
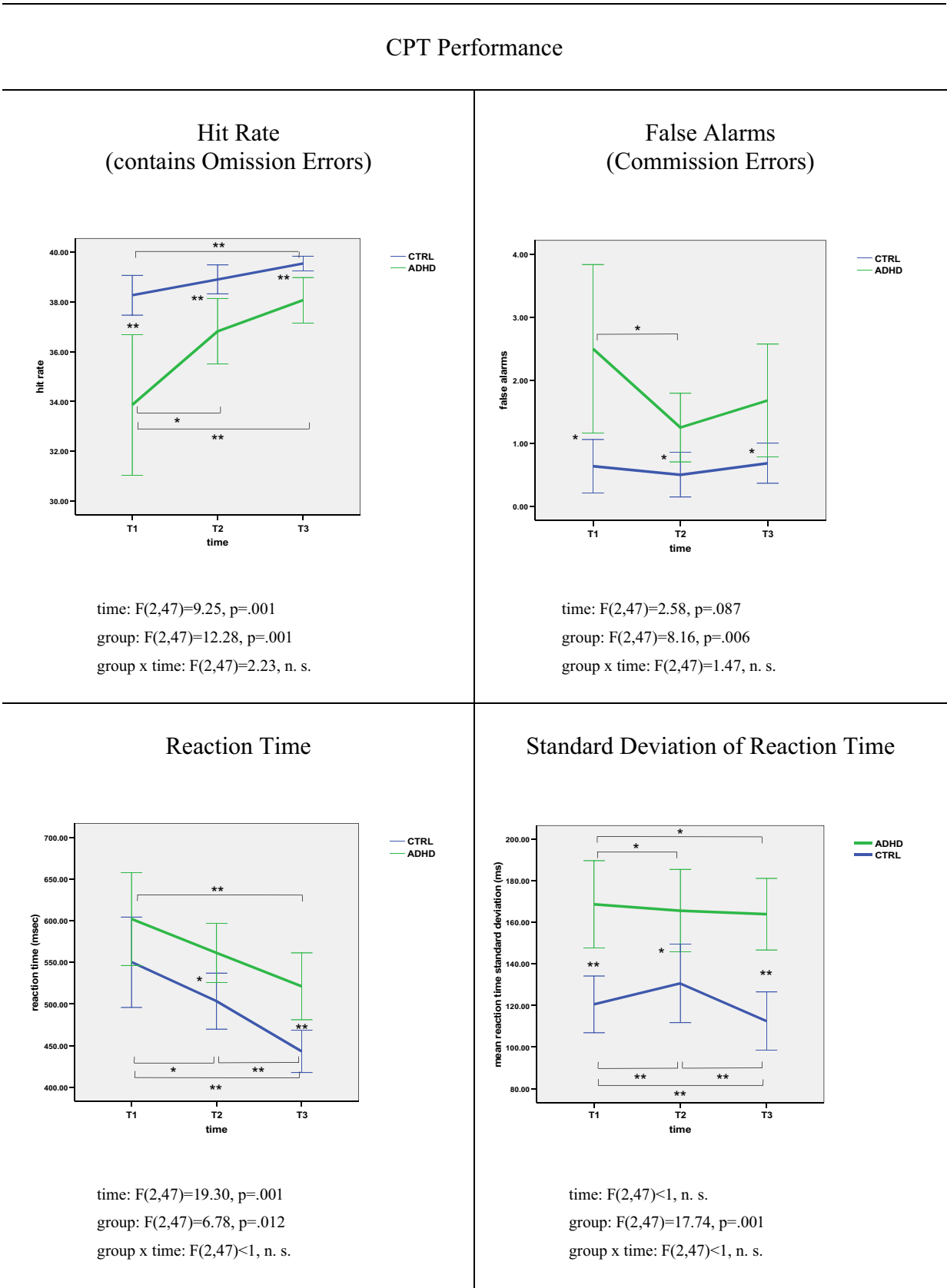


Figure 2



* $p<0.05$, ** $p<0.01$, error bars ± 2 standard errors

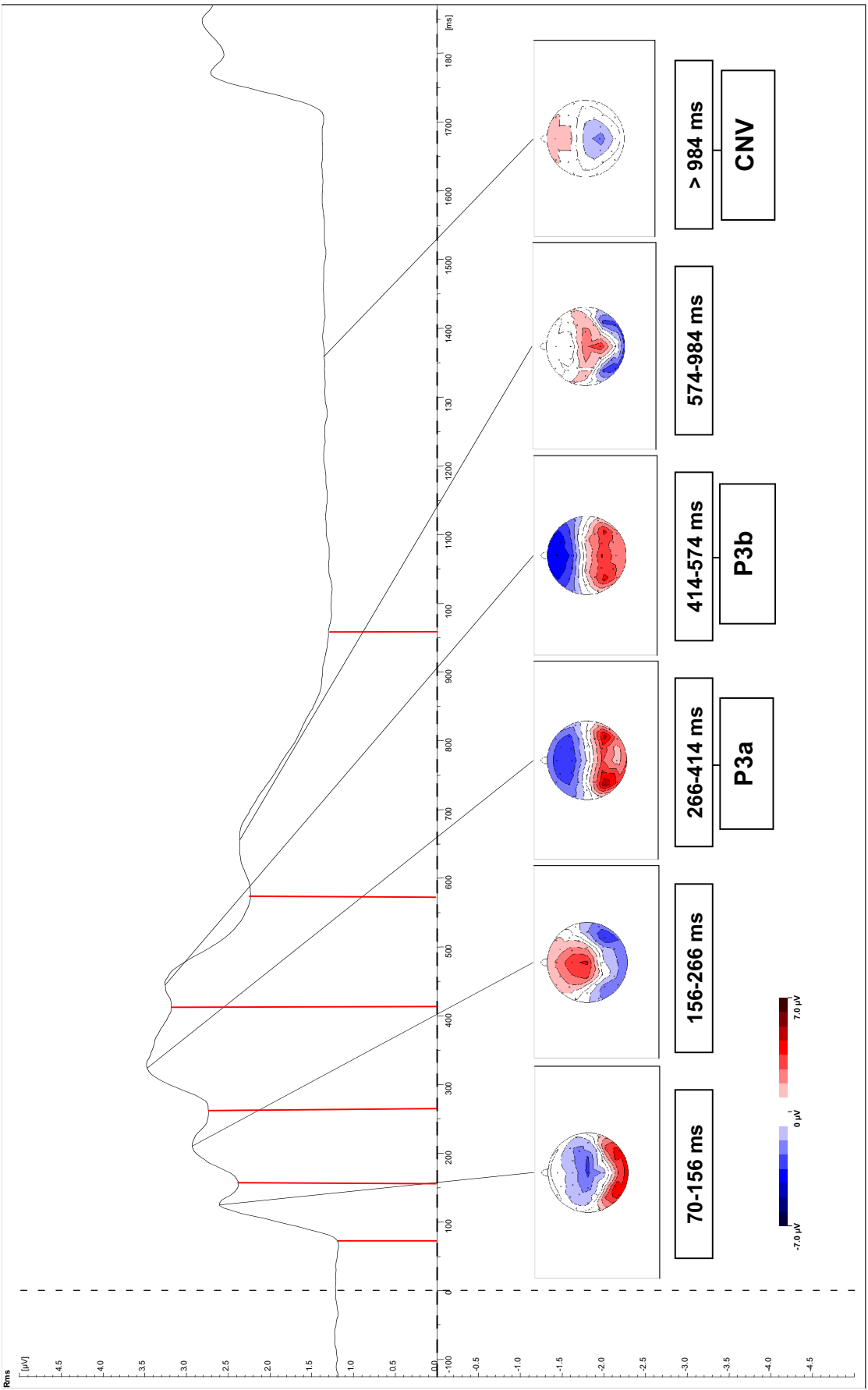
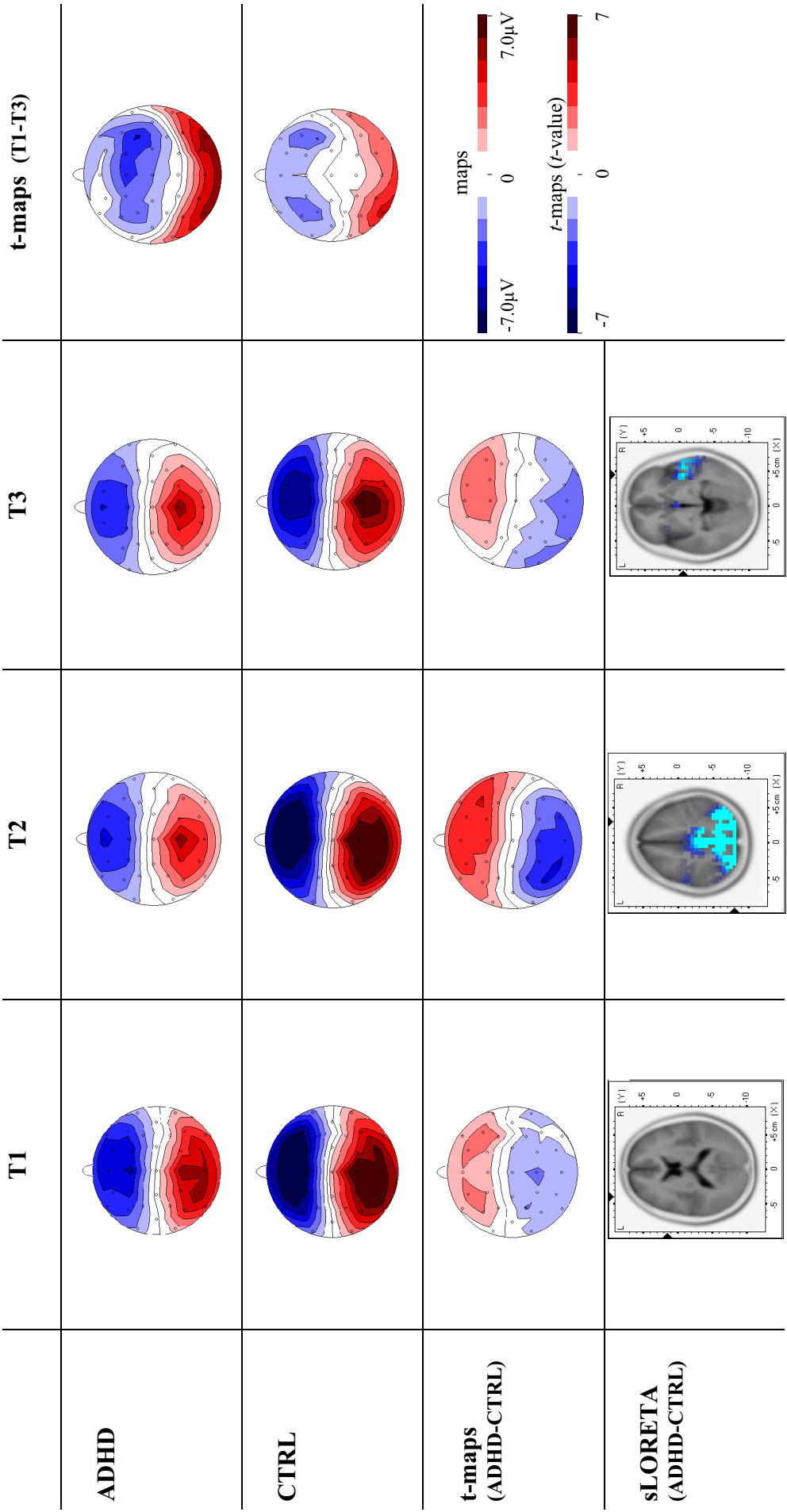


Figure 3

Figure 4



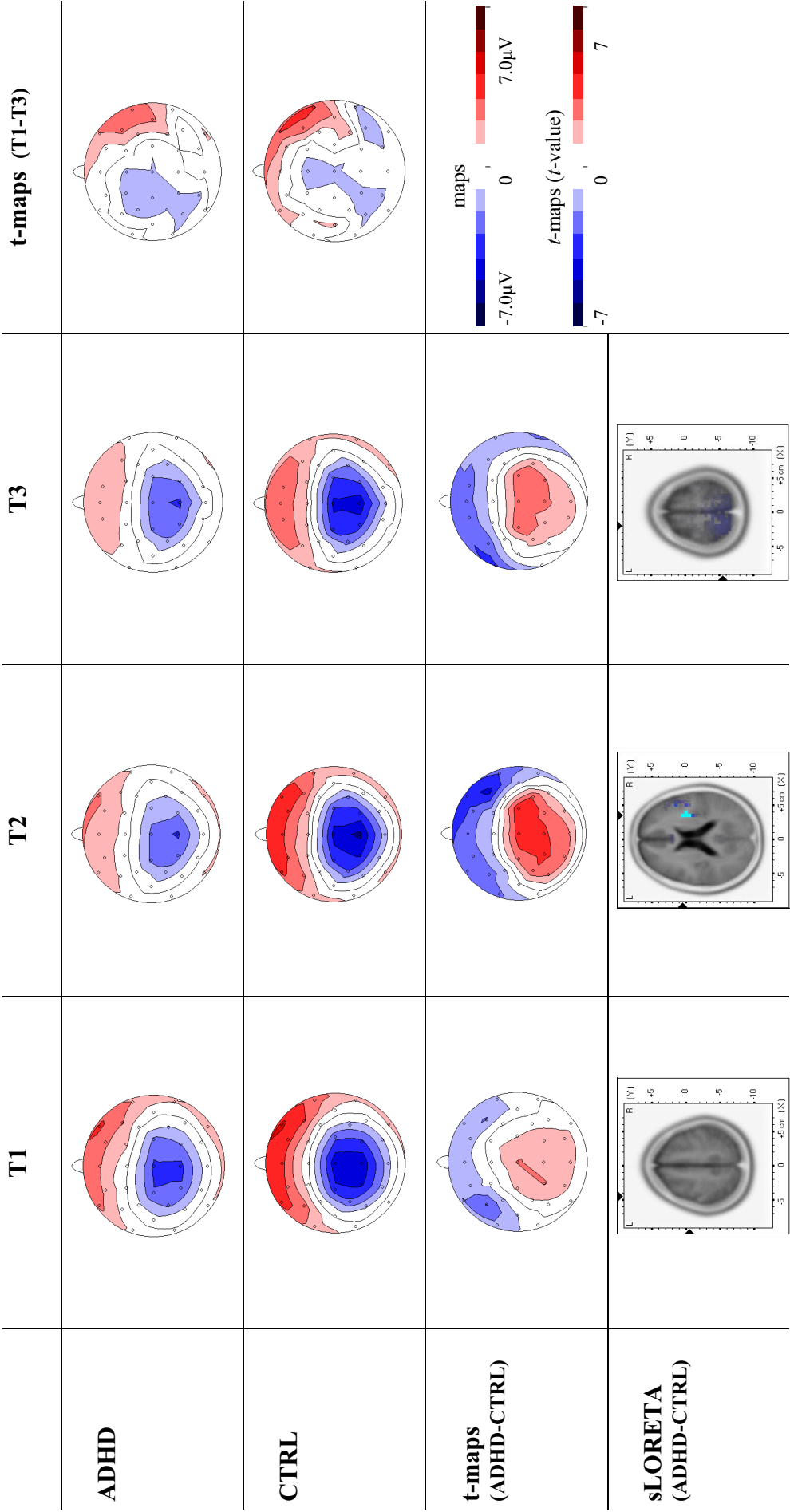
sLORETA MNI coordinates, values and significant log of F-ratios at $p < 0.05$ for the two-tailed test (SNR 100)

T1: MNI (X= -40 , Y= 15 , Z= 15), value=-7.89E-1 , significant log of F-ratio=1.150

T2: MNI (X= 30 , Y= -80 , Z= 45), value=-1.17E+0 , significant log of F-ratio=0.977

T3: MNI (X= 43 , Y= -5 , Z= -5), value=-1.14E+0 , significant log of F-ratio=1.142

Figure 5



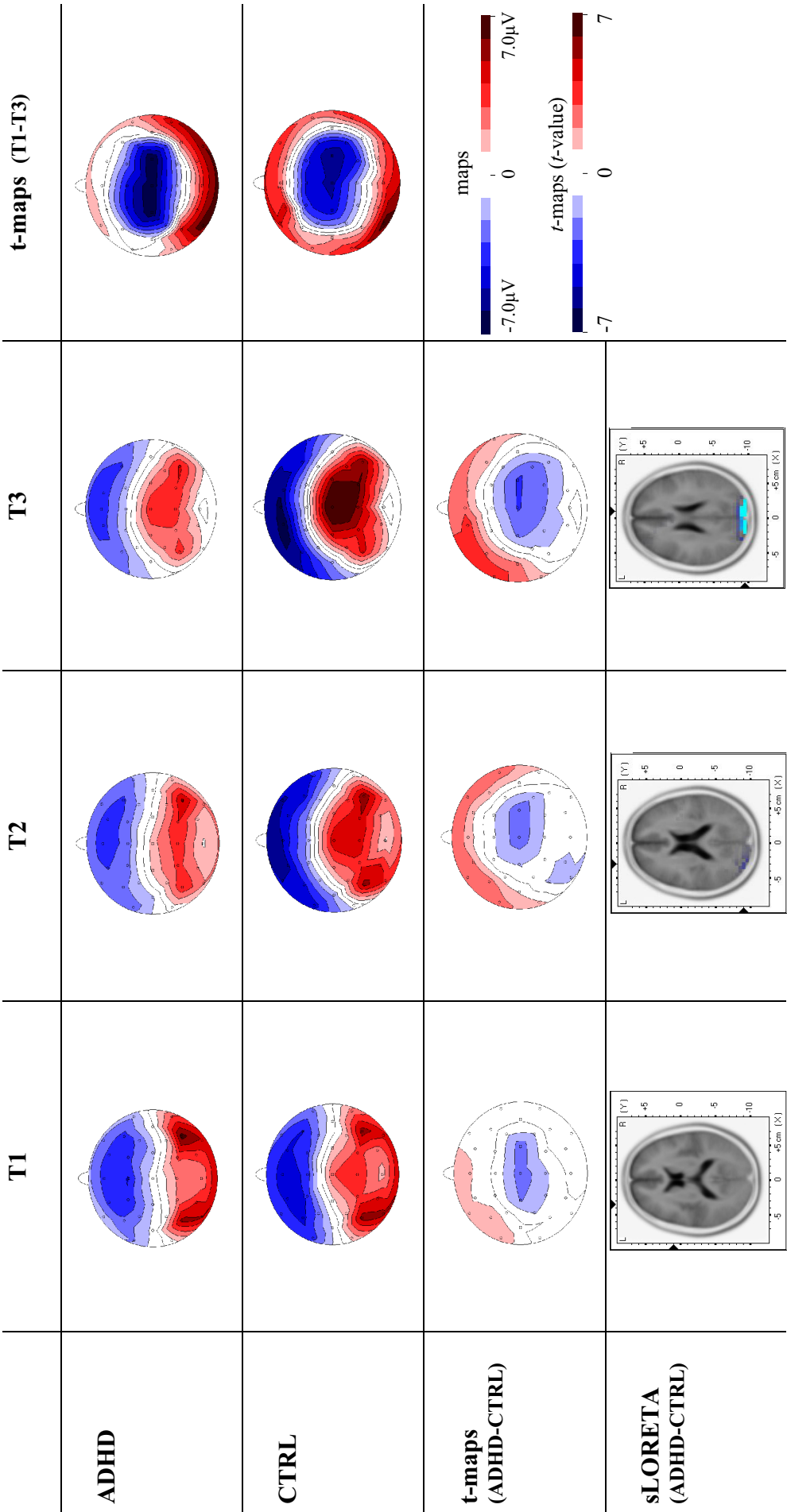
sLORETA MNI coordinates, values and significant log of F-ratios at $p < 0.05$ for the two-tailed test (SNR 100)

T1: MNI (X= -45 , Y= -5 , Z= 55), value=-7.24E-1, significant log of F-ratio=1.090

T2: MNI (X= 35 , Y= 5 , Z= 20), value=-8.40E-1, significant log of F-ratio=0.780

T3: MNI (X= -20 , Y= -55 , Z= 65), value=-8.25E-1, significant log of F-ratio=0.928

Figure 6



sLORETA MNI coordinates, values and significant log of F-ratios at $p < 0.05$ for the two-tailed test (SNR 100)

T1: MNI (X= -35 , Y= 10 , Z= 15), value=-5.64E-1 , significant log of F-ratio=0.993

T2: MNI (X= -30 , Y= -90 , Z= 20), value=-7.57E-1 , significant log of F-ratio=0.829

T3: MNI (X= 10 , Y= -95 , Z= 25), value=-1.11E+0 , significant log of F-ratio=1.036

Table 1

	ADHD	CONTROLS	t / p
N (female)	28 (3)	22 (5)	n. s.
Age mean (SD) T1	10.8 (1.7)	10.4 (1.1)	n. s.
T2	12.0 (1.8)	11.5 (1.1)	n. s.
T3	13.3 (1.8)	12.8 (1.2)	n. s.
IQ (SD)	97.4 (12.5)	109.5 (12.1)	t=3.44 / p<.001
CBCL attention problems ¹			
T-score (SD) T1	67.4 (6.3)	43.0 (5.1)	t=14.71 / p<.001
T2	62.9 (8.1)	45.1 (6.0)	t=8.49 / p<.001
T3	62.9 (8.4)	43.6 (6.0)	t=8.74 / p<.001
CBCL externalizing ²			
T-score (SD) T1	66.6 (9.2)	46.0 (7.2)	t=8.60 / p<.001
T2	62.9 (11.8)	43.4 (7.7)	t=6.63 / p<.001
T3	59.8 (10.9)	41.9 (7.5)	t=6.54 / p<.001
CBCL internalizing ³			
T-score (SD) T1	58.4 (9.0)	46.4 (7.9)	t=4.90 / p<.001
T2	55.3 (10.6)	46.8 (7.6)	t=3.12 / p<.01
T3	52.9 (11.1)	44.4 (8.8)	t=2.90 / p<.01

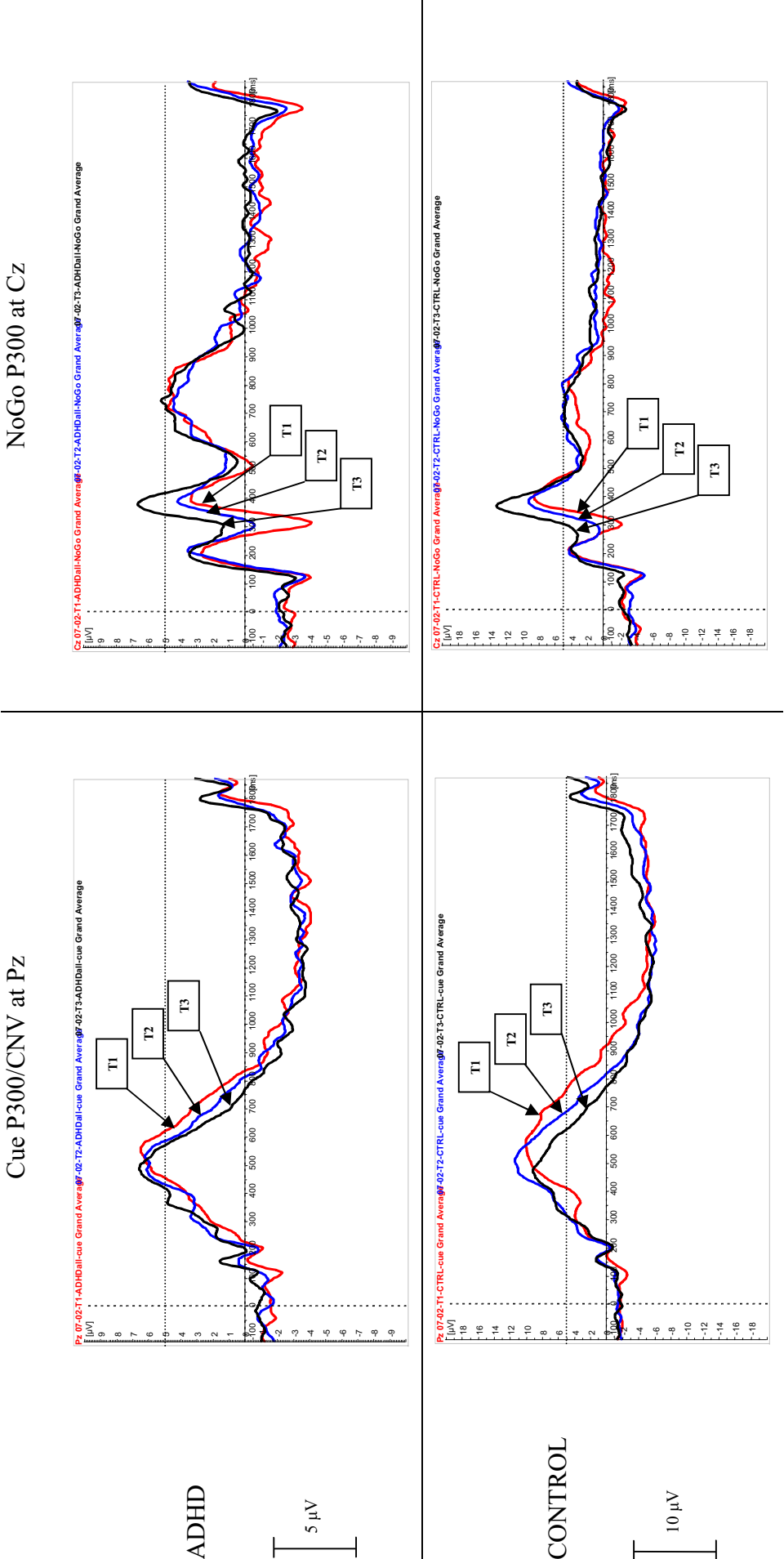
¹ Repeated measures ANOVA for CBCL attention problems: significant main effect for group $F(1,44)=128.06, p<0.001$

² Repeated measures ANOVA for CBCL externalizing: significant main effect for group $F(1,46)=64.81, p<0.001$ and for time $F(2,45)=12.01, p<0.001$

³ Repeated measures ANOVA for CBCL internalizing: significant main effect for group $F(1,46)=16.44, p<0.001$ and for time $F(2,45)=3.59, p<0.05$

Supplementary Figure 1. Selected ERP Waveshapes

Figure 1. ERP grand average waveshapes from all assessments (T1 red, T2 blue, T3 black) for the Cue- (left, at Pz) and NoGo-conditions (right, at Cz) in ADHD (top) and control subjects (bottom). Note the dashed horizontal line at 5µV marking different y-axis scales for ADHD vs CONTROL.



Supplementary Figure 2 – GFP

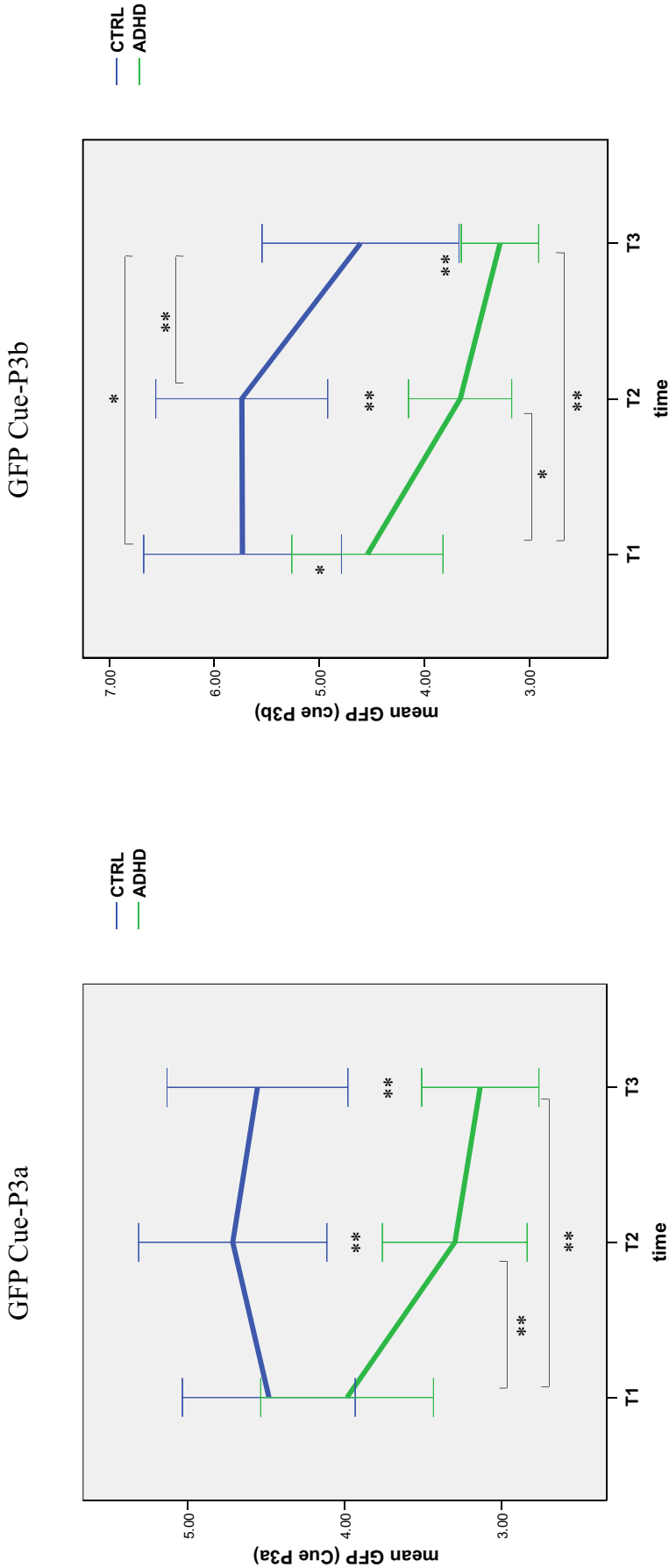


Figure 2a. GFP for Cue P300 (microstate P3a and P3b)

Post hoc *t*-tests: * $p < 0.05$, ** $p < 0.01$, error bars ± 2 standard errors

Repeated measures ANOVA for P3a: significant main effect for group ($F[1,48]=15.098, p=0.001$)

with IQ as covariate: significant main effect for group ($F[1,47]=12.923, p=0.001$); significant group x time interaction ($F[2,46]=4.436, p=0.017$)

Repeated measures ANOVA for P3b: significant main effect for group ($F[1,48]=14.303, p=0.001$); significant main effect for time ($F[2,47]=11.268, p=0.001$); significant group x time interaction ($F[2,47]=3.376, p=0.043$)

with IQ as covariate: significant main effect for group ($F[1,47]=10.034, p=0.003$); significant group x time interaction ($F[2,46]=4.017, p=0.024$)

Supplementary Figure 2 – GFP

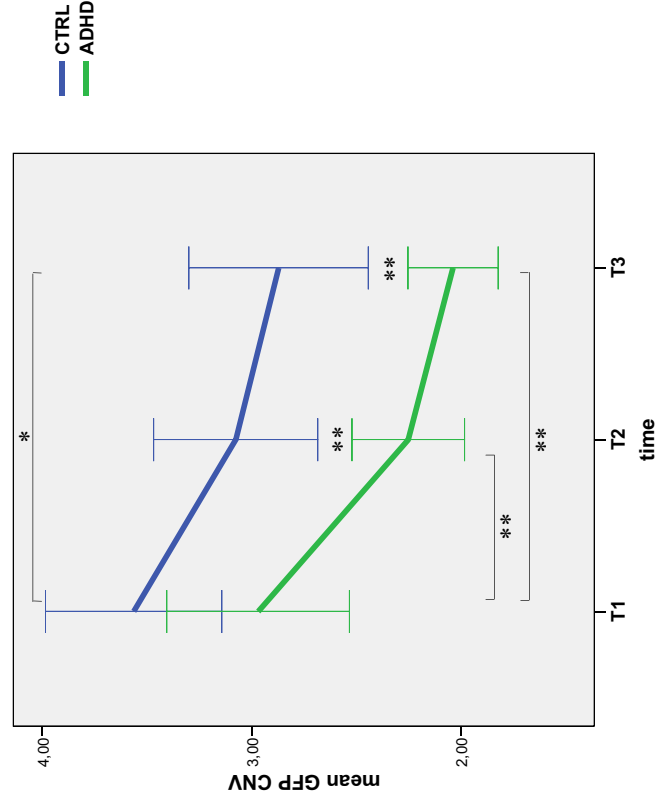


Figure 2b. GFP for CNV (1'000-1'600ms)

Post hoc *t*-tests: * $p < 0.05$, ** $p < 0.01$, error bars ± 2 standard errors

Repeated measures ANOVA: significant main effect for group ($F[1,48] = 13.693$, $p = 0.001$); significant main effect for time ($F[2,47] = 13.067$, $p = 0.001$) with IQ as covariate: significant main effect for group ($F[1,47] = 13.255$, $p = 0.001$)

Supplementary Figure 2 – GFP

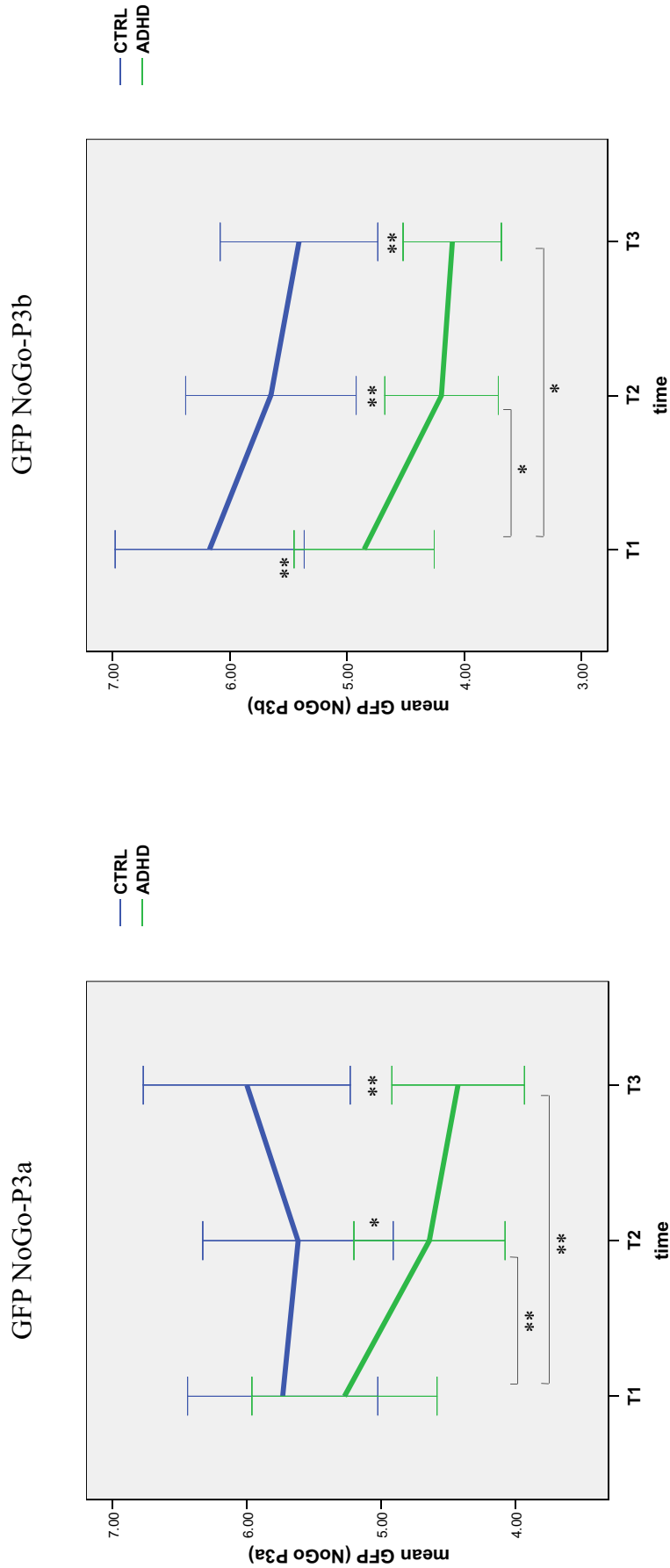


Figure 2c. GFP for NoGo P300 (microstate P3a and P3b)

Post hoc *t*-tests: * $p < 0.05$, ** $p < 0.01$, error bars ± 2 standard errors

Repeated measures ANOVA for P3a: significant main effect for group ($F[1, 48] = 12.427, p = 0.011$); significant group \times time interaction ($F[2, 47] = 3.714, p = 0.032$) with IQ as covariate; significant main effect for group ($F[1, 47] = 5.186, p = 0.003$); trend for group \times time interaction ($F[2, 46] = 2.521, p = 0.091$)

Repeated measures ANOVA for P3b: significant main effect for group ($F[1, 48] = 16.303, p = 0.001$); significant main effect for time ($F[2, 47] = 5.445, p = 0.007$) with IQ as covariate; significant main effect for group ($F[1, 47] = 18.850, p = 0.001$)

Supplementary Figure 3 – sLORETA

Figure 3a. sLORETA source localization for Cue-P3b – for both groups (ADHD vs CTRL) and all three assessments (T1-T3) sLORETA statistics comparing the Cue-related activation for P3b microstate of ADHD and control subjects at all assessment. Blue color indicates the localization of significantly reduced activity of the ADHD children compared to controls. Endpoints of scales for group comparison meet significant log of F-ratios at $p < 0.05$ for the two-tailed test

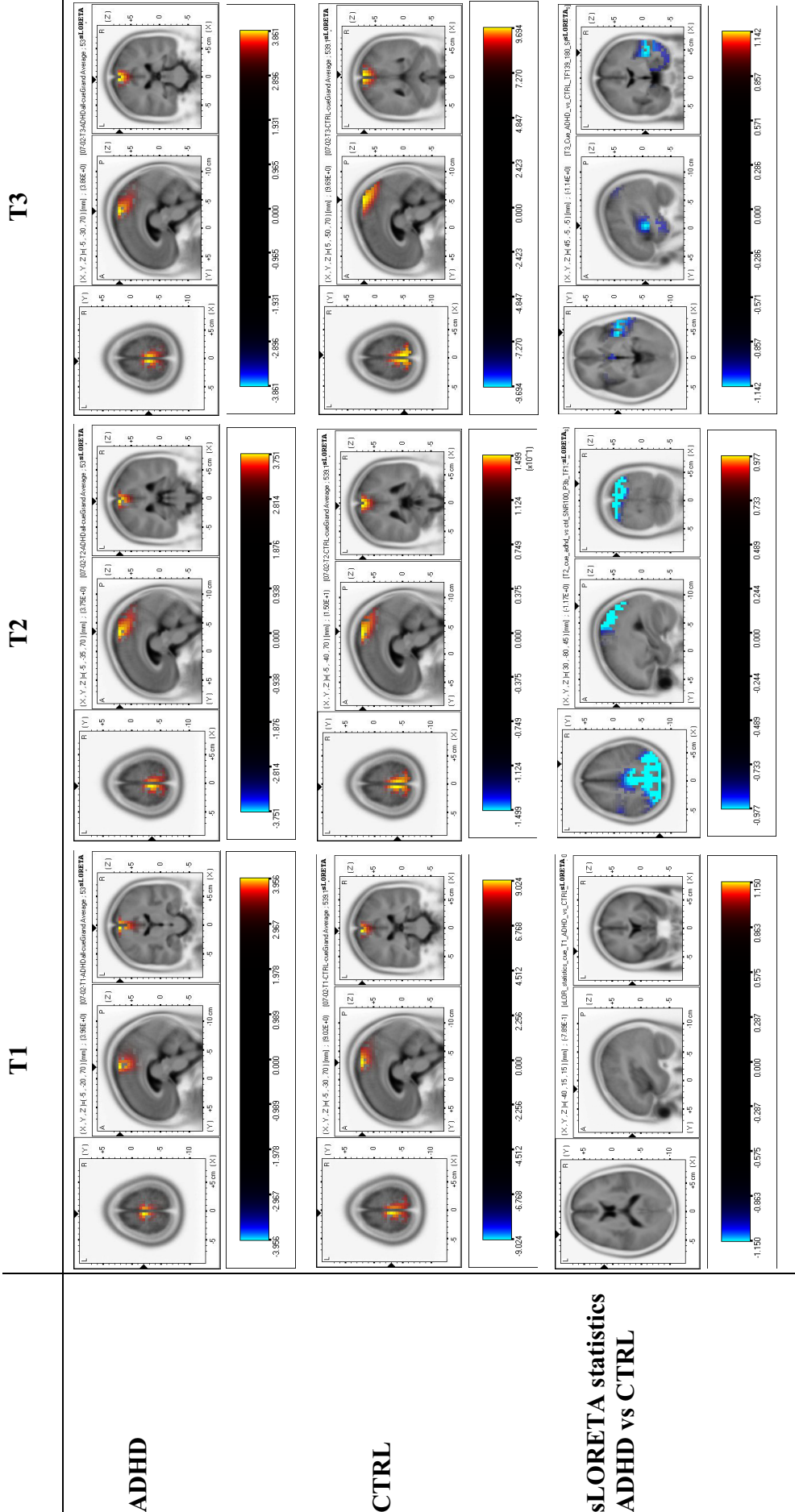


Figure 3b. sLORETA source localization for CNV (1'000-1'600ms) for both groups (ADHD vs CTRL) and all three assessments (T1-T3) sLORETA statistics comparing the CNV-related activation for ADHD and control subjects at all assessment. Blue color indicates the localization of significantly reduced activity of the ADHD children compared to controls. Endpoints of scales for group comparison meet significant log of F-ratios at $p < 0.05$ for the two-tailed test

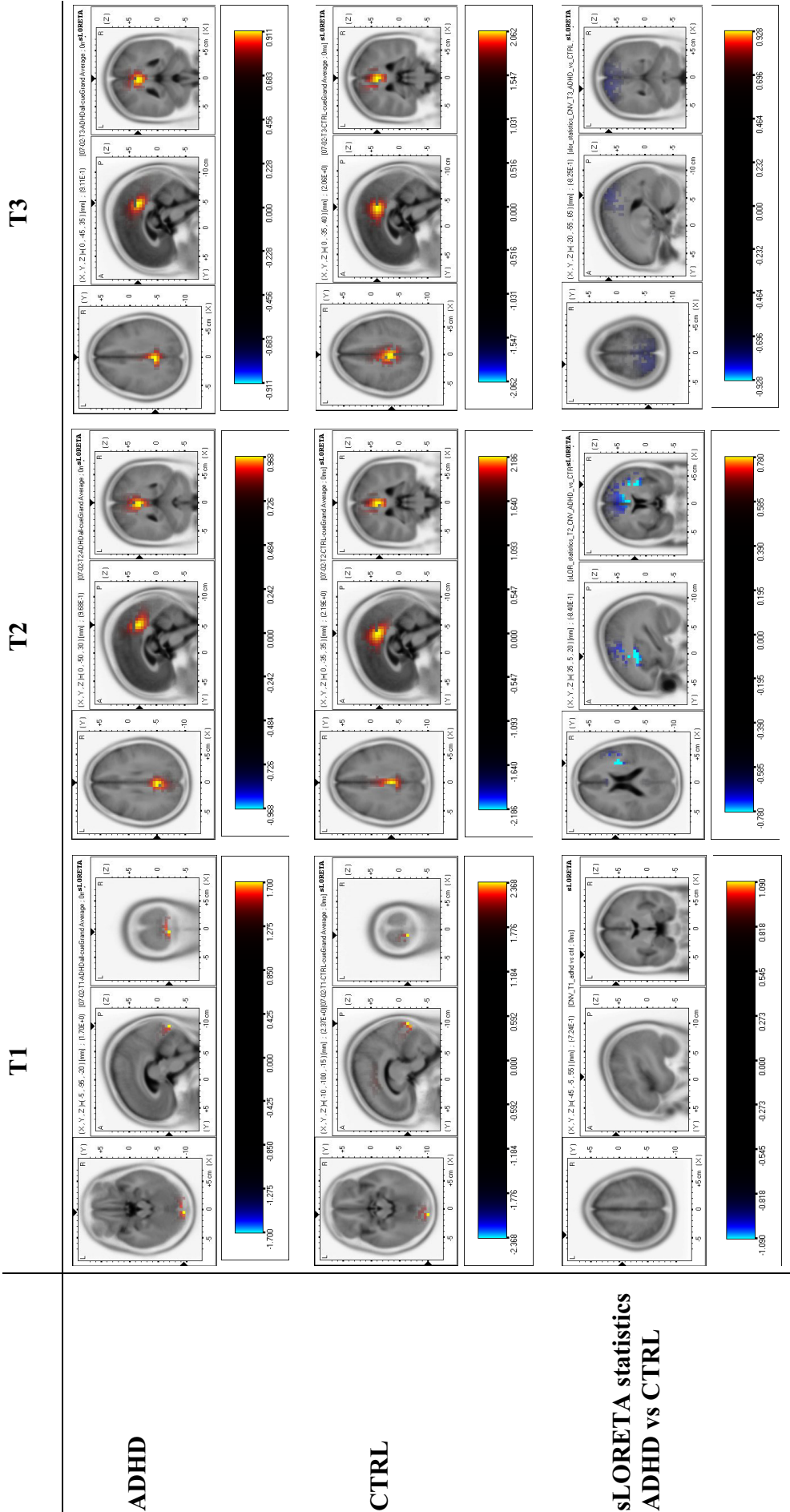
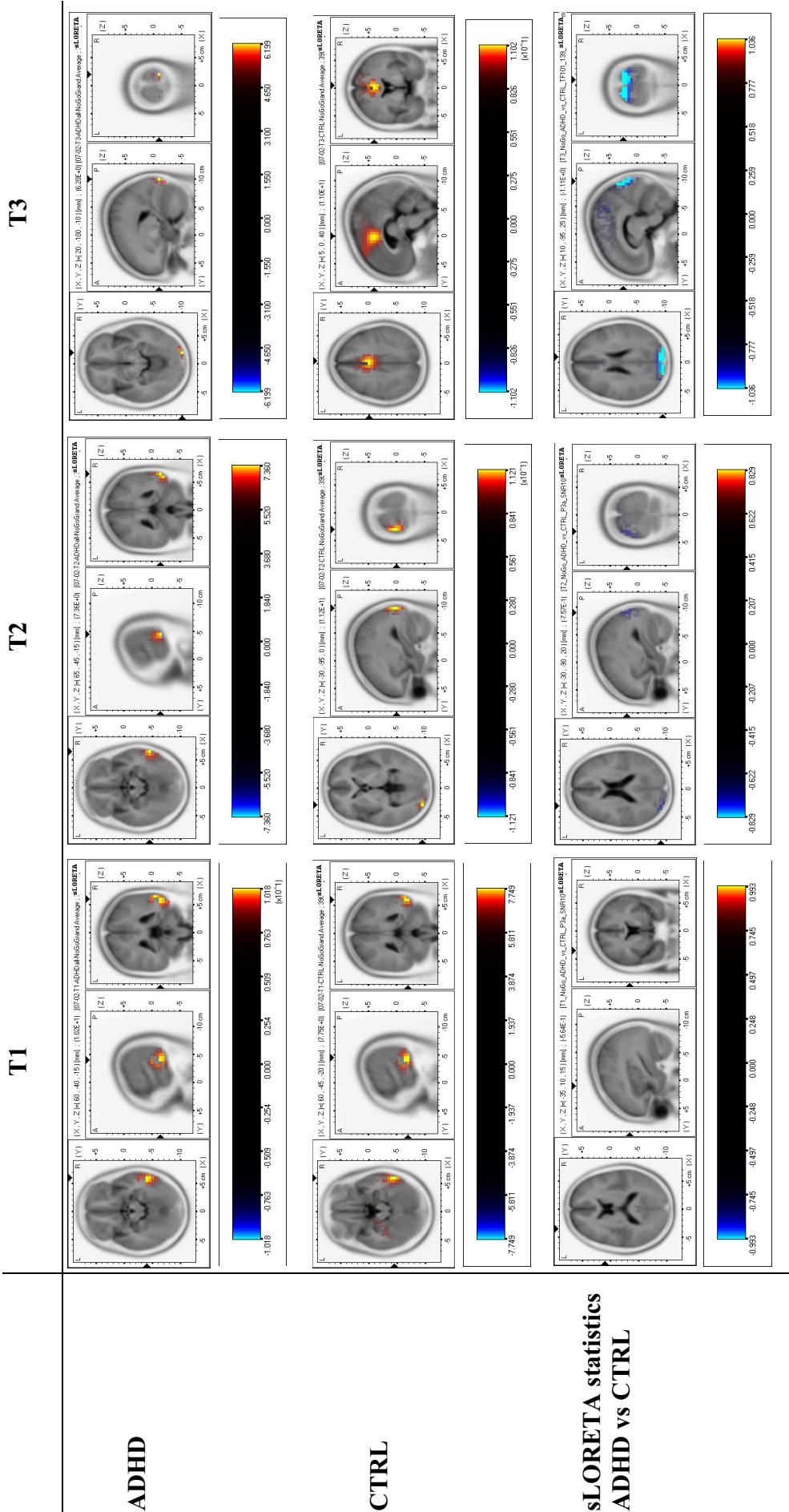


Figure 3c. sLORETA source localization for NoGo-P3a – for both groups (ADHD vs CTRL) and all three assessments (T1-T3) sLORETA statistics comparing the NoGo-related activation for P3a microstate of ADHD and control subjects at all assessment. Blue color indicates the localization of significantly reduced activity of the ADHD children compared to controls. Endpoints of scales for group comparison meet significant log of F-ratios at $p < 0.05$ for the two-tailed test



Supplementary Table 1. CPT performance

Table 1. CPT performance – ANOVA with IQ as covariate

CPT performance			
repeated measures ANOVA / IQ as covariate			
hit rate	false alarms	reaction time	
time: F(2,46)=6.02, p=0.005	time: F(2,46)=1.21, n. s.	time: F(2,46)=1.49, n. s.	
group: F(1,47)=3.95, p=0.053	group: F(1,47)=4.02, p=0.051	group: F(1,47)=2.33, n. s.	
group x time: F(2,46)=1.12, n. s.	group x time: F(2,46)<1, n. s.	group x time: F(2,46)<1, n. s.	
IQ: F(1,47)=11.10, p=0.002	IQ: F(1,47)=1.72, n. s.	IQ: F(1,47)=3.98, p=0.052	

MANCOVA (time x group x measures; IQ=covariate). Significant effect for IQ (F(3,45)=4.085, p=0.012)

Supplementary Table 2. Peak latency and amplitude

Table 2a. Cue P300 - peak latency and amplitude at Pz

Cue P300						
repeated measures ANOVA						
peak latency			peak amplitude			
time: F(2,47)=9.32, p=0.001			time: F(2,47)=2.49, n. s.			
group: F(1,48)=1.53, n. s.			group: F(1,48)=11.30, p=0.002			
group x time: F(2,47)=1.41, n. s.			group x time: F(2,47)=2.24, n. s.			
post hoc <i>t</i> -tests						
peak latency (msec)			peak amplitude (μV)			
ADHD	CTRL	<i>t</i> /p	ADHD	CTRL	<i>t</i> /p	
T1	507.39 (93.75)	554.15 (81.79)	1.85 / 0.070	8.81 (4.32)	11.98 (5.61)	2.26 / 0.028
T2	482.84 (87.41)	490.23 (80.72)	0.31 / 0.760	8.24 (3.85)	13.32 (5.80)	3.71 / 0.001
T3	469.17 (73.44)	479.94 (86.78)	0.48 / 0.637	8.01 (3.38)	11.19 (4.95)	2.70 / 0.010

Table 2b. NoGo P300 - peak latency and amplitude at Cz

NoGo P300				
repeated measures ANOVA				
peak latency		peak amplitude		
time: F(2,47)=5.35, p=0.008		time: F(2,47)=10.48, p=0.001		
group: F(1,48)<1, n. s.		group: F(1,48)=14.72, p=0.001		
group x time: F(2,47)<1, n. s.		group x time: F(2,47)<1, n. s.		

post hoc <i>t</i> -tests				
peak latency (msec)		peak amplitude (µV)		
	ADHD	CTRL	<i>t/p</i>	
T1	410.30 (36.20)	408.91 (40.31)	-0.13 / 0.899	ADHD: 5.80 (6.58) CTRL: 11.72 (6.94) <i>t/p</i> : 3.08 / 0.003
T2	399.27 (37.43)	397.90 (35.32)	-0.13 / 0.896	ADHD: 6.30 (4.48) CTRL: 11.69 (6.88) <i>t/p</i> : 3.34 / 0.002
T3	394.53 (40.89)	378.73 (36.13)	-1.43 / 0.160	ADHD: 8.91 (5.50) CTRL: 14.77 (6.85) <i>t/p</i> : 3.35 / 0.002